Dilated cardiomyopathy due to type II X-linked 3-methylglutaconic aciduria: successful treatment with pantothenic acid

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Abstract

A case of dilated cardiomyopathy in a young boy secondary to type II 3-methylglutaconic aciduria is described. A metabolic cause for his dilated cardiomyopathy was suspected because of the development on the electrocardiogram of an unusual "camel's hump" shape of the T waves, and of progressive thickening with increasing echogenicity of the left ventricular wall. He initially improved on digoxin treatment, but did not maintain the response with conventional dietary treatment for this condition. Supplementation with L-carnitine was associated with rapid deterioration in cardiac state, and may be contraindicated in this condition. At a point when the patient was moribund, large doses of pantothenic acid, a precursor of coenzyme A, produced a dramatic and sustained improvement in myocardial function and in growth, neutrophil cell count, hypocholesterolaemia, and hyperuricaemia, which suggests that limitation of availability of coenzyme A is a fundamental pathological process in this condition. The clinical improvement has been maintained for 13 months, and myocardial function is now nearly normal. Oral pantothenol, unlike pantothenic acid, is not efficacious.

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Accordingly, suggested dietary treatment is entirely empirical. We describe here the electrocardiographic features and the response to various dietary modifications and supplements in a case presenting with neonatal heart failure.

Case report

A boy with a birth weight of 2.76 kg was born after prolonged labour; frequent fetal bradycardias necessitated a ventouse extraction. Apgars were 9, 10, 10. There were no immediate neonatal problems, but he was readmitted to hospital with gross congestive heart failure at the age of 3 weeks. Chest x ray film showed considerable cardiomegaly and the electrocardiogram showed right atrial hypertrophy, left ventricular dominance with dominant S in V1, 12 mm R in V6, and generalised T wave flattening. Initial echocardiography showed a normal cardiac anatomy but grossly dilated right and left ventricles with a severely reduced left ventricular ejection fraction (22%) and severe, presumed functional, incompetence of both tricuspid and mitral valves. The coronary arteries were normal, and there were no strong endocardial echoes typical of endocardial fibroelastosis. His mother had had a viral illness two to three weeks before delivery and the differential diagnosis was thought to be "transient myocardial ischaemia of the newborn" or perinatal myocarditis. The baby was treated by rapid oral loading with digoxin, frusemide, and spironolactone and his clinical condition rapidly improved. Viral studies from mother and infant were negative.

After one month of digoxin treatment his ejection fraction had improved to 49%, and both tricuspid and mitral valve incompetence had disappeared. The T waves on the electrocardiogram were generally more upright (fig 1(A)). The ejection fraction continued to improve reaching a peak of 59% at 6 months of age (fig 2(A)) and it was thought likely that his cardiomyopathy was due to a perinatal insult. Initial weight gain was relatively satisfactory with weight remaining on the third centile and height along the 10th centile, but around 6 months of age weight gain began to fall off the third centile (fig 2(C)) and height and head circumference dropped to the third centile. There were no symptoms or signs of congestive heart failure. He was a poor eater, taking only small amounts of solids, and often had respiratory tract infections. After 12 months of age the electrocardiogram started to show increasing T wave abnormalities with

In 1991 Kelley *et al* described the association of a dilated cardiomyopathy with growth failure, neutropenia, and a low serum cholesterol occurring in five pedigrees with an inheritance suggestive of an X linked disorder.¹ The disorder was associated with increased urinary excretion of 3-methylglutaconic and 3-methylglutaric acids. Subsequently the condition has been separated from other phenotypic manifestations of more severe 3-methylglutaconic aciduria and termed the type II syndrome.² Death may occur from heart failure or sepsis in early life, but survival to late childhood and possibly adulthood in untreated patients has been reported.¹ 3-Methylglutaconate is an intermediate in the catabolism of leucine, but whereas the primary metabolic defect in type I 3-methylglutaconic aciduria has been described—namely, 3-methylglutaconic coenzyme A hydrolase deficiency—no specific defect in the type II presentation has as yet been identified.¹

Figure 1 (A) Development of T wave abnormalities and left ventricular hypertrophy in the period before pantothenic acid treatment. The first line of complexes shows the electrocardiogram at presentation with heart failure at 3 weeks of age. The T waves are generally flat, the QT interval 0.32 s and QTc 0.46s. Sokolow-Lyon index (S in V_1 plus R in V_6) = 30 mm. The second line of complexes shows the electrocardiogram at three months of age; T waves are more normal but the R wave in V_6 is increased at 24 mm. The QT interval is 0.29 s and QTc 0.43s. Sokolow-Lyon index = 36 mm. The third line of complexes shows the electrocardiogram at the age of 18 months, shortly before the diagnosis was made. The appearance of the T wave is unusual with a very early onset of the T wave, only 0.06 s after the beginning of the QRS complex, and with a camel's hump notch after the maximum T wave amplitude. The QT interval is 0.30 s and QTc remains long at 0.44s. Thus there is increasing difference in the duration of the action potential in different parts of the myocardium with some areas having a very short duration. Sokolow-Lyon index = 46 mm. The fourth line shows the electrocardiogram at the age of 22 months, on dietary treatment, but before starting pantothenic acid. The T waves are still notched, but generally flatter so that the duration of the QT interval is difficult to measure accurately; the QTc seems shorter than before at about 0.39s. There is considerable increase in voltages with a Sokolow-Lyon index of 58 mm. Over the next two months there was a dramatic further increase in voltages with the Sokolow-Lyon index reaching 93 mm. **(B)** Gradual normalisation of the electrocardiographic voltages and the improvement in T wave abnormalities after the start of treatment with pantothenic acid. The first line shows the electrocardiogram two months after the start of pantothenic acid. The onset of the T wave is no longer so early, starting 0.13 s after the onset of the QRS complex. The QT interval is 0.33 s and QTc 0.46s. Sokolow-Lyon index = 72 mm. The second line shows the electrocardiogram after six months of pantothenic acid. T waves are still visibly notched, the QT interval is 0.35 s and QTc 0.45s. Sokolow-Lyon index = 98 mm. The third line shows the electrocardiogram after nine months of treatment. The QT interval is 0.35 s and QTc now normal at 0.41s. Sokolow-Lyon index = 55 mm. The fourth line shows the most recent electrocardiographic recording, taken after 13 months of treatment with pantothenic acid. T wave notching is still visible in V_6 , but QTc = 0.41s and Sokolow-Lyon index = 38 mm are now both within the normal range.

a "camel's hump" type biphasic T wave and an early onset of the T wave, (fig 1(A)), progressive T wave inversion and increasing left ventricular voltages. Echocardiography showed increasing echodensity in the inner third of the posterior left ventricular wall, and a slight fall off in ejection fraction to 49% (fig 2(A)). This prompted further investigations to look for a metabolic cause for his cardiomyopathy.

Before the results of the investigations were available his myocardial function deteriorated. The ejection fraction fell to 30% and mitral incompetence reappeared. Captopril was started with transitory improvement in ejection fraction. A preliminary report suggested that serum free carnitine concentrations were low. Accordingly he was given dietary supplements of L-carnitine in an initial dose of 30 mg/kg/day increasing to 90 mg/kg/day. This

Figure 2 Effect of drug treatments and diets on the patient's myocardial function, neutrophil white cell count, and weight gain. The starts of different treatments are indicated with arrows labelled D, digoxin; A, captopril; C, carnitine supplement; L, low protein diet; P, pantothenic acid supplement. Carnitine supplement was stopped at the arrow L, when moderate protein restriction was started.

(A) Ejection fraction (EF), left ventricular end diastolic diameter (LVEDD), and posterior left ventricular wall thickness (PLVW). Note the rapid fall in EF and rapid increase in LVEDD seen with the carnitine supplement (arrow C), and the fact that despite progressive dilatation of the left ventricle the posterior left ventricular wall thickness did not decrease, but increased, indicating rapid increase in left ventricular mass. Conversely, after pantothenic acid (arrow P), increase in EF and the reduction in LVEDD is accompanied by a gradual reduction in left ventricular wall thickness.

(B) Total white cell and neutrophil count. Note the brief improvement in total white cell count, and in absolute neutrophil count after the start of the low protein diet (arrow L). This was not sustained. Before the pantothenic acid supplement the neutrophil count ranged between 9–15% of the total white cell count. After pantothenic acid treatment was started the neutrophil count ranged between 16% and 45% of the total white cell count, and has remained $> 1.3 \times 10^9/l$.

(C) Patient's weight gain plotted on a standard centile chart. Note the weight loss after the start of a diet with moderate protein restriction (arrow L), and the sustained catch up growth that followed the start of the pantothenic acid supplement. Initially the same protein restrictions were adhered to, so the weight gain is not due to increased protein intake. The moderate restrictions of protein intake have been relaxed over the last six months, but the patient's spontaneous intake does not exceed 2.5 g/kg/day.

was not associated with clinical improvement. On the contrary there was a close temporal association with reduction in ejection fraction, an increase in left ventricular end diastolic diameter, increase in absolute left ventricular wall thickness (fig 2(A)), and an increase in mitral incompetence. With the Devereux formula³ for echocardiographic estimation of left ventricular mass it was estimated that there had been a 59% increase in left ventricular mass over the seven weeks of carnitine treatment. At this point his cardiac state was precarious, and a heart transplant was being considered. He was admitted to hospital for further metabolic studies.

Results

Other than the abnormalities already described, clinical examination was unremarkable. In particular, formal neurological assessment showed no evidence of cognitive

or motor deficits and muscle tone was normal.

Investigations showed the following: haemoglobin 11.6 g/dl, white cell count $5.5 \times 10^9/l$ (neutrophils 10.4%, $0.57 \times 10^9/l$), platelets $278 \times 10^9/l$, mean corpuscular volume 75 fl, urea 11.9 mmol/l, creatinine 71 $\mu\text{mol/l}$, urate 569 $\mu\text{mol/l}$, albumin 37 g/l, bilirubin $< 17 \mu\text{mol/l}$, aspartate aminotransferase 74 IU/l, creatine kinase 71 IU/l, total cholesterol 2.2 mmol/l, serum lactate 1.45 mmol/l. Serum iron and total iron binding capacity were normal. Urinary organic acids showed moderately increased excretion of 3-methylglutaconic, 3-methylglutaric, and 2-ethylhydracrylic acids. Thus on the basis of the presence of the organic aciduria, low absolute neutrophil count, hypocholesterolaemia,¹ and hyperuricaemia,⁴ a diagnosis of type II X linked 3-methylglutaconic aciduria was strongly suggested.

A survey of the scientific literature suggested that the dietary manipulations that had been used with possible anecdotal benefit were: (a) medium chain triglyceride supplement, (b) moderately reduced protein intake, and (c) cholesterol supplement.¹ Thus the carnitine supplement was stopped, and a controlled protein diet (2 g/kg/day) with a supplement of medium chain triglycerides was started. In the next two weeks on this diet there was a dramatic improvement in appetite and general level of physical activity, a moderate rise in white blood cell and absolute neutrophil count (fig 2(B)), and a moderate improvement in ejection fraction (fig 2(A)). The left ventricle remained dilated and mitral valve incompetence remained severe. Then, inexplicably, after six weeks the patient's appetite deteriorated and he started to lose weight (fig 2(C)). Cholesterol supplement, in the form of egg yolks, was started, but his condition continued to deteriorate.

A multi vitamin and mineral supplement (Seravit) was prescribed. Two weeks after the addition of Seravit he was found to have a severe haemolytic anaemia with haemoglobin of 6.7 g/dl. He was transfused, but continued to haemolyse and required daily transfusions. On the suspicion of glucose-6-phosphate dehydrogenase deficiency, Seravit, which contains vitamins C and K, was stopped, and the haemolysis ceased abruptly. Subsequent investigations showed normal glucose-6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase activities, and no unstable haemoglobins were present. A direct Coombs test was negative. Surprisingly, the patient's red cells were more resistant to osmotic stress than control cells. He continued to lose weight and overnight tube feeding, large doses of vitamin B complex (nicotinamide, pyridoxine, riboflavin, and thiamine), and a gradual increase in medium chain triglyceride supplement failed to halt his decline (fig 2(A) and 2(B)). He was virtually moribund with pulmonary oedema, gross hepatic enlargement, severe oliguria, and an ejection fraction of 14%.

At this point it was conjectured that as the excretion of 3-methylglutaconic acid was only

moderate, the metabolite was probably derived from a small body pool rather than a large body pool as in the type 1 syndrome. Furthermore, as 3-methylglutaconic acid derives from the coenzyme A ester, there could be a consequent sequestration of coenzyme A in a small, specific body pool. Given the overriding cardiac presentation of the patient, this pool might be the myocardium. Sequestration of coenzyme A might compromise that organ's ability to oxidise its normal metabolic fuels, namely free fatty acids and glucose, giving rise to impaired cardiac contractility.

The patient's diet was therefore changed. The principles were to reduce the leucine content (the milk formula changed to Paedisure), to reduce the medium chain triglyceride supplement, to add carbohydrate supplement, and to change the vitamin supplement from Vitamin B compound Strong to a preparation that contained pantothenic acid, the precursor of coenzyme A. The only commercial preparation available containing large amounts of pantothenic acid was the intravenous preparation Solivito N which was given orally. The response was dramatic: the child started to pass urine, overt heart failure disappeared over two days, and the ejection fraction improved to 28%. The improvement was maintained and his appetite improved. Subsequently, we attempted to move to a commercial oral vitamin preparation, but could identify only one containing large doses of any derivative of pantothenic acid, namely Vigranon B. This contains racemic pantothenol (panthenol), the alcohol derivative of pantothenic acid. This was fed together with other vitamin supplements to give at least equivalent vitamin supplements to that obtained from Solivito N. Two days after changing to pantothenol, however, the child was in gross heart failure again and was unresponsive to parenteral diuretics. The next day he remained gravely ill and pantothenol was changed to pantothenic acid (Solivito N) again. There followed a steady and maintained improvement. As the only relevant change in his diet at this time was the exchange of pantothenic acid for panthenol, and there was no intercurrent illness to account for his deterioration, it seemed that he was unable to use pantothenol, the alcohol form of the coenzyme A precursor.

After his recovery we have now introduced oral pantothenate as the pure hemicalcium salt (Sigma chemicals), gradually increasing the dose from 15 mg/day to 50 mg three times daily. Other vitamin supplements consist of Abidec (0.3 ml twice daily), Vitamin B compound Strong (one tablet daily), and folic acid (2.5 mg once daily). Water and fruit juices are supplemented with Maxijul to a 13.5%–18% of the carbohydrate concentration and the protein restriction has gradually been relaxed. On this regimen the boy's appetite is good, his weight gain has improved (fig 2(C)), and his cardiac function has shown a sustained improvement with left ventricular ejection fraction improved to 52%, gradual disappear-

ance of left ventricular dilatation (fig 2(A)), and eventual complete disappearance of mitral incompetence. Furthermore echocardiographic estimates suggests a 65% reduction in left ventricular mass since the start of the pantothenic acid supplement. The start of the pantothenic acid supplement was also associated with a considerable increase in neutrophil count (fig 2(B)), both absolute and as percentage of total white cell count. Hypcholesterolaemia and hyperuricaemia have also improved (cholesterol 4.0 mmol/l; uric acid 149 μ mol/l).

Discussion

We present a child with type II X linked 3-methylglutaconic aciduria who showed no sustained improvement in cardiac function despite conventional dietary and drug treatment. The introduction of pantothenic acid to the therapeutic regimen resulted in a dramatic clinical improvement. This therapeutic approach was based upon the hypothesis that there was a compromised tissue supply of coenzyme A, perhaps particularly affecting the heart's ability to use its main metabolic fuels—namely free fatty acids and glucose. There are several possible mechanisms that might explain the efficacy of pantothenic acid. They include: (a) Abnormalities, possibly tissue specific, of the coenzyme A biosynthetic pathway. Most likely this would affect the rate limiting pantothenic acid kinase⁵ in such a way that adequate flux along the pathway could only occur in the presence of a very high concentration of substrate. This is a recognised mechanism in other vitamin responsive errors of metabolism; (b) Tissue specific sequestration of coenzyme A as the methylglutaconyl thioester or other non-metabolisable intermediates; (c) Enhanced degradation of coenzyme A.

Data we have available do not allow any distinction between these possibilities. It is noteworthy that pantothenol was not efficacious. This may well reflect the lack of alcohol dehydrogenase in the heart⁶ and the adverse redox state and metabolic insufficiency within the liver of a child in gross heart failure. The rapidity of the deterioration after switching to pantothenol renders it unlikely that failure to absorb the compound from the intestinal tract played a significant part.

The initial daily dose of pantothenic acid that was associated with a clinical improvement was 5–8 times the normal dietary intake of infants, and the currently used dose is about 30 times the recommended minimum daily intake for adults.⁷ Excess dietary pantothenic acid is excreted in the urine,⁸ and since treatment started we have found increased pantothenate in the child's urine (unpublished observations). Daily doses of up to 10 g of calcium pantothenate are free of toxic effects.⁹

CARNITINE

It is often stated that a supplement of L-carnitine is totally without risks or side effects, and

that it might be beneficial not only in primary carnitine deficiency, but also in secondary carnitine deficiencies—for example, organic acidurias such as 3-methylglutaconic aciduria.¹⁰ In this boy, however, several clinical variables showed accelerated deterioration with the carnitine supplement. In particular, there was a rapid increase in left ventricular wall thickness as well as left ventricular end diastolic diameter. As both were reversible with pantothenic acid supplement it suggests that there was an accumulation of some intermediate metabolite within the myocardium.

L-Carnitine is an essential cofactor in the translocation of free long chain fatty acids into the mitochondrial matrix,¹¹ and this process also requires cytoplasmic fatty acylcoenzyme A, whereas subsequent intramitochondrial catabolism of fatty acids requires coenzyme A. Thus if the availability of coenzyme A is limited, a dietary supplement of L-carnitine alone will not lead to any clinical improvement. Indeed, the possible production and accumulation within the mitochondria of abnormal metabolites may lead to a deterioration in tissue functions as occurred here, and the thickening of the left ventricular wall may reflect just such a process. Hence, it would seem prudent to exclude 3-methylglutaconic aciduria and perhaps other organic acidurias, before therapeutic trials with L-carnitine are attempted in cases with dilated cardiomyopathy of possible metabolic origin.

DIGOXIN

It is a recurrent finding from previous case histories that digoxin has a clearly beneficial effect on myocardial contractility in 3-methylglutaconic aciduria.¹ This effect has been strikingly shown in this case too, although the initial improvement in ejection fraction from 22% to 59% (fig 2(A)) was not maintained when the left ventricular wall started to show pathological thickening, presumably caused by accumulation of abnormal metabolites.

The responsiveness to digoxin, together with the oddly shaped T waves on the electrocardiogram, lead us to consider whether 3-methylglutaconic aciduria is associated with abnormalities in plasma membrane sodium-potassium ATPase. Screening for the efficacy of the ATPase by subjecting red cells to osmotic stress showed the reverse, namely that this patient's red cells show a reduced sensitivity to osmotic stress, a finding that at the moment remains unexplained, but is particularly interesting in relation to his haemolytic crisis.

DRUG INDUCED HAEMOLYSIS

Initially we suspected that the boy's haemolysis was due to glucose-6-phosphate dehydrogenase deficiency as this is also an X linked

condition. Further investigations have, however, shown normal glucose-6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase activities. Thus both the mechanism and the agent in the Seravit preparation responsible for the episode of haemolysis remain unknown. It is, however, unlikely to have been caused by vitamins C or D, or the B complex vitamins as the patient continues to tolerate normal or increased doses of these in other vitamin preparations.

In conclusion there is little doubt that large doses of pantothenic acid (a precursor of coenzyme A) were life saving in this patient. Provision of this rate limiting substrate for coenzyme A synthesis has led to improvement not only in myocardial contractility, but also to neutrophil cell counts and hypocholesterolaemia, suggesting that limitation of availability of coenzyme A is a fundamental pathological process in type II 3-methylglutaconic aciduria. As shown here a sustained improvement can be obtained with manipulation of the diet and a supplement of pantothenic acid and the condition is notably responsive to digoxin treatment. Thus, all cases of idiopathic dilated cardiomyopathy ought to be screened for metabolic causes. In particular, male patients of all ages should be screened for 3-methylglutaconic aciduria. Associated features suggesting the diagnosis include neutropenia, hypocholesterolaemia, and hyperuricaemia.

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